Original Article

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Effects of exercise on reducing diabetes risk in Korean women according to menopausal status

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Background: Exercise and estrogen play key roles in preventing diabetes and obesity. Women's risk of diabetes could increase due to the loss of the protective effect of estrogen after menopause. Therefore, we investigated the relationship of the intensity and frequency of exercise with diabetes risk in Korean women.

Methods: Hazard ratios (HRs) for the development of diabetes were analyzed in 926,807 premenopausal and 1,188,346 postmenopausal women without diabetes over the age of 40 who underwent the Korean National Health Examination in 2009 and were followed up until 2018. The number of days of physical activity according to exercise intensity and metabolic equivalent of task-minutes per week (MET-min/wk) were calculated.

Results: In total, 38,096 premenopausal (4.1%) and 120,605 postmenopausal (10.2%) women were newly diagnosed with diabetes. Regardless of menopausal history, the risk of diabetes was significantly lower in groups with higher MET-min/wk than in sedentary participants (0 MET-min/wk, reference), although this effect disappeared in postmenopausal women with the highest level of MET-min/wk (MET-min/wk ≥1,500) after adjusting for all variables (HR, 1.0; 95% confidence interval, 0.97–1.02). Participants who exercised for more than 1 day per week had a significantly lower risk of diabetes, regardless of the intensity. However, this benefit was lost in women with near-daily exercise (≥6 days/wk).

Conclusions: Exercise was effective in preventing diabetes in both premenopausal and postmenopausal women. A moderate amount of exercise should be actively encouraged to lower the risk of diabetes in women, especially after menopause, while simultaneously considering the insignificant benefits of excessive exercise.

Keywords: Exercise; Diabetes mellitus; Women; Menopause; Postmenopause

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INTRODUCTION

Exercise plays a key role in preventing obesity by increasing blood flow to adipose tissue and inducing fat mobilization. Exercise consumes fatty acids by inducing their transfer from adipose tissue to skeletal muscle and improves adipose tissue metabolism by alleviating hypoxia and reducing the local inflammatory response [1]. Exercise also induces weight loss, increases muscle mass and glucose uptake in muscles, enhances the action of insulin, improves insulin resistance with less hypoglycemia, and enhances cardiovascular function to create a healthy body in the long run [2]. Therefore, the current guidelines recommend regular physical activity for the prevention of diabetes, with moderate exercise of 150 minutes or more and vigorous exercise of 75 minutes or more a week [3,4]. Despite these advantages of exercise, less than half of women were found to be physically active [5]. An observational study of more than 70,000 Korean women found that only one-third walked regularly [6]. According to the Diabetes Fact Sheet of the Korean Diabetes Association published in 2020 [7], the prevalence of diabetes among women in their 40s is 3.5%, but there is a steep upward trend in its prevalence, which reaches more than 10% in women over 50, corresponding to the age range when women generally enter menopause.

Estrogen plays a protective role against obesity by regulating food intake and energy expenditure, body fat accumulation via lipolysis with or without lipogenesis control, and inflammatory pathways in adipose tissue [8]. Weight gain is primarily attributable to the aging process rather than estrogen depletion after menopause, but changes in body composition and fat distribution occur as an independent effect of menopause [9]. In addition to preventing changes in body composition in ways that are detrimental to glucose metabolism, there are several possible mechanisms through which estrogen can directly contribute to improving glucose homeostasis and preventing diabetes, including improvements of insulin sensitivity and lipogenic pathways, control of hepatic gluconeogenesis, and enhancement of beta-cell function and survival in pancreatic islet cells [10,11].

Although no consensus exists regarding whether menopause independently increases the risk of diabetes [9,12], many clinical studies have reported that hormone replacement therapy in postmenopausal women consistently lowers blood glucose and reduces the risk of developing diabetes [13,14]. The protective effect of estrogen could also be inferred from studies stating that the early onset of menopause increases the risk of diabetes in postmenopausal women [15,16]. Regular exercise in postmenopausal women could improve insulin sensitivity and beta-cell function and mass [17]. In addition, adequate physical activity is important for postmenopausal women to prevent changes in body composition that make them vulnerable to metabolic risk [18]. Higher-volume aerobic exercise has additional benefits in lowering the total body and subcutaneous abdominal fat, especially in obese postmenopausal women [19]. Many studies have provided evidence supporting the proposal that exercise can prevent diabetes in postmenopausal women [20,21]. However, contrary to those studies, Hsia et al. [22] published research with more than 90,000 multiethnic menopausal women suggesting that the association between exercise and a reduced risk of diabetes was not statistically significant after adjusting for age and multiple risk factors except in Caucasians. Interestingly, it was observed that in Asians, the hazard ratio (HR) for diabetes was higher in the quintile that exercised the most than in more sedentary quintiles, unlike other ethnicities that showed a trend for risk reduction with increasing exercise.

Therefore, we investigated the effects of exercise in postmenopausal women, who are exposed to a greater risk of diabetes than premenopausal women, using data from Korean women who underwent health insurance screening through the National Health Insurance Service (NHIS).

METHODS

The NHIS database

The NHIS, a government agency that implements a medical insurance system for all Koreans, manages a database containing individual medical records, including hospital visits, diagnoses of diseases, performed tests, and prescriptions of medications. In addition to these data, records of regular (annual to biennial) health examinations for adults over 40 years and workers over 20 years were merged. These health screening databases include anthropometric measurements and personalized questionnaires, such as past medical history; information on drinking, smoking, and physical activity; and laboratory findings. The NHIS has processed and distributed all these databases for use in cohort studies [23].

This study was approved by the NHIS and the Institutional Review Board of Kangbuk Samsung Hospital (No. KBSMC 2021-04-049). The data are converted by deleting individuals' names and IDs and encrypted, so there is no risk of exposing individuals' personal information. Therefore, informed consent was not required.

Study participants

This study included Korean women over 40 years of age who underwent an examination through the Korean National Health Screening program in 2009 (n=3,109,506). Among them, participants who had already undergone hysterectomy (n=314,529), had missing data (n=432,111), had been diagnosed with diabetes (n=237,949), and were diagnosed with diabetes within 1 year of participating in the study (n=9,764) were excluded. Following this exclusion process, 926,807 premenopausal and 1,188,346 postmenopausal women with a confirmed menstrual history were included in the study. These participants were followed up until December 31, 2018 (Fig. 1).

Definition of exposure and outcome

The exercise history was determined by participants' answers to a self-questionnaire on the number of exercise sessions, days, and the intensity of physical activity. The intensity of physical activity consists of three categories: vigorous exercise (running, aerobics, fast cycling, field work, and carrying heavy objects on the stairs), moderate exercise (brisk walking, tennis, cycling at normal speed, carrying light objects, and cleaning), and walking. Regular exercise was defined as moderate exercise for more than 5 days per week or vigorous exercise for more than 3 days per week. In addition, metabolic equivalents-minutes per week (MET-min/wk) were calculated based on the results of the questionnaire. MET values of 2.9, 4.0, and 7.0 were assigned for walking, moderate exercise, and vigorous exercise, respectively [24]. We divided participants into five groups of exercise volume according to MET-min/wk (0, 0–500, 500–1,000, 1,000–1,500, and ≥1,500) with 500–1,000 MET-min/wk defined as the normal range, since the current guideline for exercise recommends 500 to 1,000 MET-min/wk [3].

Diabetes was defined as a blood sugar level of 126 mg/dL or higher according to the Clinical Practice Guideline for Diabetes by the Korean Diabetes Association [25], a response of "yes" to the item asking "Do you have diabetes?" on the self-questionnaire, a medical history in the NHIS database with International Classification of Diseases, 10th revision (ICD-10) codes of E11 to E14, or a history of being prescribed antidiabetic medications during follow-up. If the participant was diagnosed with diabetes, follow-up was terminated.

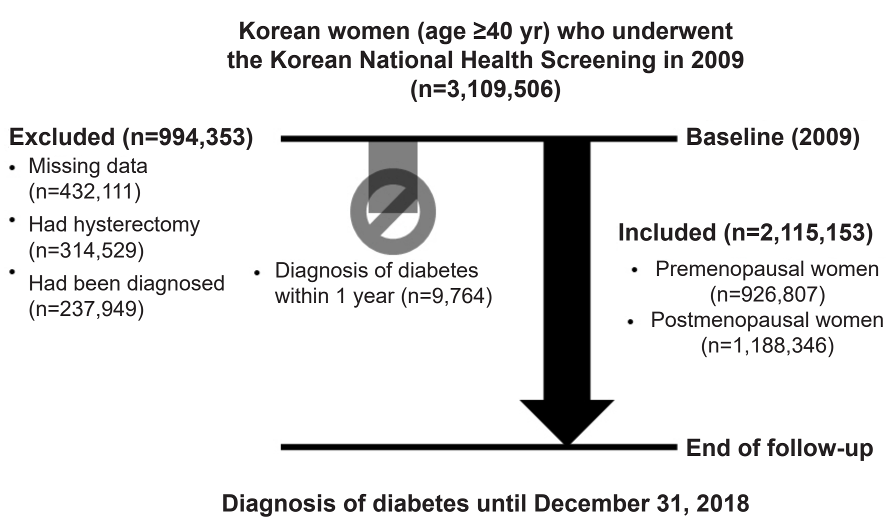

Fig. 1. Flowchart of the enrollment of study participants.

Statistics

We analyzed the effect of exercise on the risk of diabetes in each premenopausal and postmenopausal group using a Cox proportional hazards model with a 95% confidence interval (CI). Using the sedentary group (0 MET-min/wk) as a reference, the HRs of each exercise volume group were analyzed to confirm the difference in risk. Additionally, the risk differences according to the number of days of each degree of exercise intensity (0, reference; 1–3 day/wk; 4–5 day/wk; ≥6 day/wk) were analyzed. After the calculation of crude incidence and nonadjusted HR, the variables influencing the occurrence of outcomes, such as age, smoking history (current smoking or not), drinking history (drinking more than 30 g/d or not), income (below the 20th percentile or not), body mass index (BMI), hypertension (blood pressure ≥140/90 mmHg, ICD-10 codes I10 to I15, or a report of antihypertensive medication usage), hyperlipidemia (total cholesterol ≥240 mg/dL, ICD-10 code E78, or a claim for antihyperlipidemic medications), and baseline blood glucose level, were included in the multivariable-adjusted analysis (model 1, nonadjusted; model 2, age; model 3, model 2+smoking history, drinking history, income; model 4, model 3+baseline BMI, hypertension, dyslipidemia, blood glucose). A subgroup analysis was also conducted, in which participants were divided into tertiles according to MET-min/wk.

Statistical analysis was performed using IBM SPSS ver. 20.0 (IBM Corp., Armonk, NY, USA). Statistical significance was set at P<0.05. The t-test or analysis of variance was performed for continuous variables, and the chi-square test or the Fisher exact test was performed for categorical variables.

RESULTS

Baseline characteristics

Of the 2,115,153 women included in the study, 926,807 were premenopausal, and 1,188,346 were postmenopausal. In 2018, 4.1% of premenopausal women (n=38,096) and 10.2% of postmenopausal women (n=120,605) were diagnosed with diabetes (Table 1). The median time to the onset of diabetes was 8.29 and 8.38 years in premenopausal and postmenopausal women, respectively. The average age of premenopausal and postmenopausal women was approximately 45 and 61 years, respectively. Baseline BMI, metabolic profiles, and the prevalence of hypertension and hyperlipidemia were all higher in postmenopausal women. The average baseline blood glucose level was 91.5±10.4 mg/dL and 93.8±11.1 mg/dL in premenopausal and postmenopausal women, respectively (P<0.001). The proportion of regular exercisers was slightly higher (17.3% vs. 18.3%) in postmenopausal women. There was no significant difference in the amount of exercise calculated by MET-min/wk between the premenopausal and postmenopausal women (P=0.556).

Risk of diabetes according to exercise

The diabetes incidence rates (per 1,000 person-years) in sedentary participants (0 MET-min/wk, reference) were 5.73 and 13.87 in premenopausal and postmenopausal women, respectively. All exercise groups showed lower incidence rates than the sedentary group (Table 2). After adjusting for all variables (model 4), the HRs of diabetes were significantly lower in the groups that achieved higher MET-min/wk than in the sedentary group regardless of the menopausal history, except in the premenopausal (HR, 0.96; 95% CI, 0.91–1.01) and postmenopausal women (HR, 1.0; 95% CI, 0.97–1.02) with the highest exercise amount (≥1,500 MET-min/wk) (Fig. 2). The greatest risk reduction was observed at 1,000 to 1,500 MET-min/wk in premenopausal (HR, 0.95; 95% CI, 0.91–0.98) and postmenopausal women (HR, 0.96; 95% CI, 0.94–0.98).

In a subgroup analysis of MET-min/wk by tertile, the HRs of diabetes were significantly lower in the tertiles with higher MET-min/wk than in the first tertile (mean MET-min/wk, 21.0±40.3 in premenopausal women and 0 in postmenopausal women; reference), regardless of the menopausal history (Table 3).

In the analysis of the number of days of exercise per week by intensity, participants who exercised for more than 1 day had a lower HR than participants who were sedentary (reference), regardless of the frequency (Table 4). However, this benefit was lost in women who engaged in near-daily (≥6 day/wk) walking (HR, 1.0; 95% CI, 0.97–1.03 in premenopausal women and HR, 1.0; 95% CI, 0.99–1.02 in postmenopausal women), moderate exercise (HR, 1.01; 95% CI, 0.96–1.07 in premenopausal women and HR, 1.05; 95% CI, 1.03–1.08 in postmenopausal women), and vigorous exercise (HR, 1.03; 95% CI, 0.97–1.10 in premenopausal women

Table 1. Baseline characteristics of the participants according to menopausal status

Menopausal status	Premenopausal (n=926,807)	Postmenopausal (n=1,188,346)	P-value
Age (yr)	45.1±4.2	61.2±8.3	<0.001
Body mass index (kg/m^2)	23.2±3.0	24.0±3.1	<0.001
Waist circumference (cm)	75.0±7.9	79.5±8.4	<0.001
Low income[a)]	238,166 (25.7)	271,208 (22.8)	<0.001
Smoking			<0.001
Non	880,964 (95.0)	1,145,050 (96.4)	
Ex	14,811 (1.6)	12,277 (1.0)	
Current	31,032 (3.4)	31,019 (2.6)	
Drinking			<0.001
Non	664,591 (71.7)	1,036,187 (87.2)	
Mild	251,766 (27.2)	146,045 (12.3)	
Heavy[b)]	10,450 (1.1)	6,114 (0.5)	
Hypertension	125,196 (13.5)	508,287 (42.8)	<0.001
Hyperlipidemia	97,171 (10.5)	373,185 (31.4)	<0.001
Systolic blood pressure (mmHg)	117.1±14.2	125.1±16.1	<0.001
Diastolic blood pressure (mmHg)	73.1±9.9	76.8±10.2	<0.001
Total cholesterol (mg/dL)	191.9±38.7	209.0±43.5	<0.001
LDL cholesterol (mg/dL)	114.5±69.9	128.2±69.2	<0.001
HDL cholesterol (mg/dL)	60.5±34.9	58.2±35.8	<0.001
Triglyceride (mg/dL)	87.7 (87.6–87.8)	113.4 (113.3–113.5)	<0.001
Fasting plasma glucose (mg/dL)	91.5±10.4	93.8±11.1	<0.001
Regular exercise[c)]	159,833 (17.3)	217,911 (18.3)	<0.001
MET-min/wk	472.8±492.1	472.4±536.9	0.556
Diagnosed with diabetes	38,096 (4.1)	120,605 (10.2)	<0.001
Median time to diagnosis (yr)	8.29	8.38	<0.001

Values are presented as mean±standard deviation, frequency (%), or mean (95% confidence interval).
LDL, low-density lipoprotein; HDL, high-density lipoprotein; MET, metabolic equivalent of task.
[a)]Defined as income below the 20th percentile; [b)]Defined as drinking more than 30 g of alcohol per day; [c)]Defined as moderate exercise more than 5 day/wk or vigorous exercise more than 3 day/wk.

and HR, 1.03; 95% CI, 1.0–1.06 in postmenopausal women) in both premenopausal and postmenopausal women, after adjusting for all variables (model 4).

DISCUSSION

This study demonstrated that exercise effectively reduced the risk of diabetes in both premenopausal and postmenopausal women, securing sufficient representation of Korean adult women over 40 years of age by enrolling more than 2 million people. Although we did not intend to study the association between menopausal status and the risk of diabetes, the incidence of diabetes more than doubled from 4% to 10% in premenopausal and postmenopausal women, respectively, in our study. Considering that the prevalence of diabetes among Korean women over 50 years is rapidly increasing [7] and that fewer than one-fifth of postmenopausal women engaged in regular exercise in our study, exercise is an important lifestyle factor that needs to be corrected to prevent diabetes in Korean postmenopausal women.

Previous studies have shown that postmenopausal women have lower exercise capacity than premenopausal women, even among healthy women [26]. Postmenopausal women are exposed to the risk of reduced exercise capacity in various ways. Reproductive and chronological aging over time in perimenopausal women was associated with substantially increased fat mass and decreased skeletal muscle mass [27]. Stimulation of estrogen receptors in the hypothalamus by estrogen could increase physical activity, an advantage difficult to obtain in postmenopausal women [28].

Table 2. IRs and multivariable-adjusted HRs (95% CI) of diabetes according to the amount of exercise (MET-min/wk)

Amount of exercise	Mean MET-min/wk	No. of participants	No. of events	IR (per 1,000 person-years)	HR (95% CI)			
					Model 1[a)]	Model 2[b)]	Model 3[c)]	Model 4[d)]
Premenopausal								
0	0	234,913	10,984	5.73	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
1–499	265.9±122.9	317,931	12,150	4.67	0.82 (0.80–0.84)	0.88 (0.86–0.90)	0.89 (0.87–0.91)	0.96 (0.93–0.98)
500–999	685.7±134.8	241,067	9,524	4.82	0.84 (0.82–0.87)	0.89 (0.86–0.91)	0.90 (0.88–0.92)	0.96 (0.93–0.99)
1,000–1,499	1202.6±152.8	92,281	3,745	4.95	0.86 (0.83–0.90)	0.89 (0.86–0.92)	0.90 (0.87–0.94)	0.95 (0.91–0.98)
≥1,500	1905.1±297.9	40,615	1,693	5.08	0.89 (0.84–0.93)	0.88 (0.84–0.93)	0.89 (0.85–0.94)	0.96 (0.91–1.01)
Postmenopausal								
0	0	375,861	40,806	13.87	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
1–499	272.4±120.2	336,125	32,931	12.4	0.89 (0.88–0.91)	0.93 (0.92–0.95)	0.94 (0.93–0.95)	0.96 (0.95–0.98)
500–999	676.5±130.3	295,705	29,331	12.53	0.90 (0.89–0.92)	0.95 (0.94–0.96)	0.95 (0.94–0.97)	0.97 (0.96–0.98)
1,000–1,499	1211.4±159.0	115,191	11,003	12.01	0.87 (0.85–0.88)	0.93 (0.92–0.95)	0.94 (0.92–0.96)	0.96 (0.94–0.98)
≥1,500	1988.5±321.6	65,464	6,534	12.57	0.91 (0.88–0.93)	0.97 (0.94–0.99)	0.97 (0.95–1.0)	1.0 (0.97–1.02)

IR, incidence rate; HR, hazard ratio; CI, confidence interval; MET, metabolic equivalent of task.
[a)]Nonadjusted; [b)]Adjusted for age; [c)]Adjusted for age, low income, smoking, and drinking; [d)]Adjusted for age, low income, smoking, drinking, hypertension, hyperlipidemia, body mass index, and baseline plasma glucose.

Table 3. IRs and multivariable-adjusted HRs (95% CI) of diabetes according to the amount of exercise (MET-min/wk) divided by tertile

Amount of exercise	Mean MET-min/wk	No. of participants	No. of events	IR (per 1000 person-years)	HR (95% CI)			
					Model 1[a)]	Model 2[b)]	Model 3[c)]	Model 4[d)]
Premenopausal								
T1	21.0±40.3	301,300	13,488	5.48	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
T2	357.9±127.4	315,858	12,030	4.65	0.85 (0.83–0.87)	0.90 (0.88–0.92)	0.91 (0.89–0.93)	0.96 (0.93–0.98)
T3	1029.6±429.6	309,649	12,578	4.96	0.90 (0.88–0.93)	0.92 (0.90–0.94)	0.93 (0.91–0.95)	0.97 (0.94–0.99)
Postmenopausal								
T1	0	375,861	40,806	13.87	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
T2	317.0±149.0	403,242	39,455	12.38	0.89 (0.88–0.90)	0.93 (0.92–0.95)	0.94 (0.93–0.95)	0.96 (0.95–0.98)
T3	1059.3±492.0	409,243	40,344	12.43	0.89 (0.88–0.91)	0.95 (0.94–0.96)	0.96 (0.94–0.97)	0.97 (0.96–0.99)

IR, incidence rate; HR, hazard ratio; CI, confidence interval; MET, metabolic equivalent of task.
[a)]Nonadjusted; [b)]Adjusted for age; [c)]Adjusted for age, low income, smoking, and drinking; [d)]Adjusted for age, low income, smoking, drinking, hypertension, hyperlipidemia, body mass index, and baseline plasma glucose.

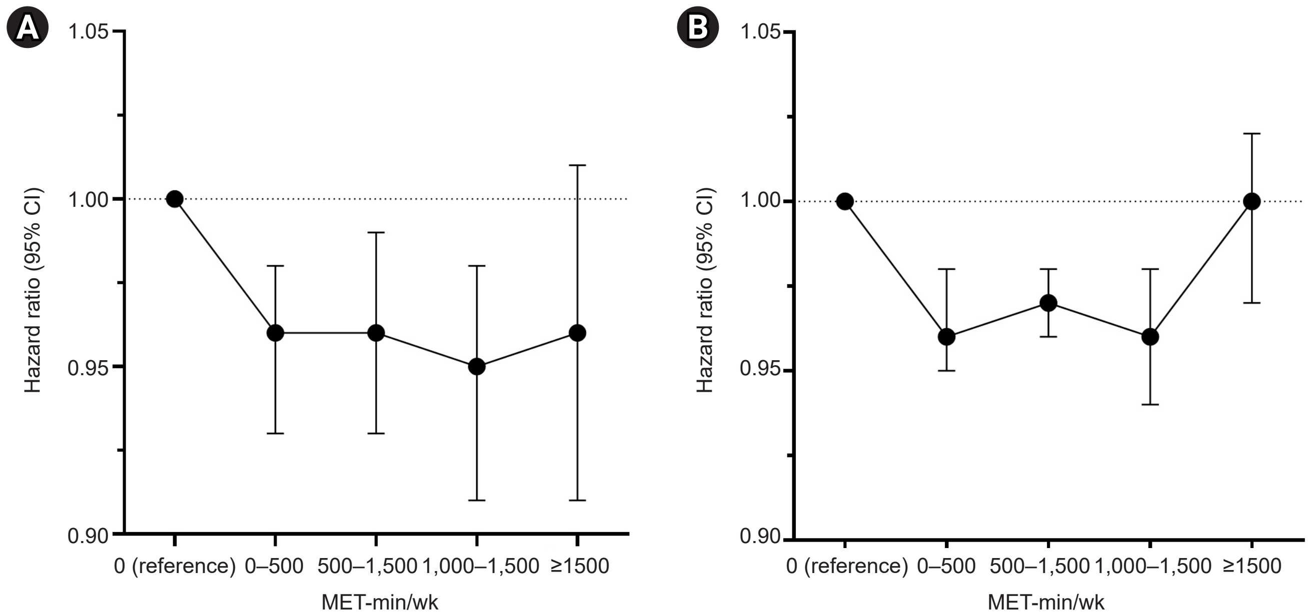

Fig. 2. Multivariable-adjusted hazard ratios (95% confidence interval [CI]) of diabetes according to the amount of exercise (metabolic equivalent of task-minutes per week [MET-min/wk]) after adjusting for all variables. (A) Premenopausal women. (B) Postmenopausal women.

Along with the natural decline in estrogen after menopause, a sedentary lifestyle and poor nutritional supplementation with insufficient protein intake reduced bone mass density, muscle mass, and strength in postmenopausal women [29]. In our study, nearly a third of postmenopausal women had a completely sedentary lifestyle, consistent with a previous study of Korean women, with nearly two-thirds not even walking regularly [6]. Moreover, we demonstrated that exercise had a significant benefit in reducing the risk of diabetes even when the amount of exercise was less than 500 MET-min/wk or simply a little more walking than a sedentary lifestyle. This is consistent with the Da Qing study [30], a representative study among Asians, where even modest changes in physical activity showed a substantial diabetes risk reduction by about 46%. Current guidelines mentioned that even small increases in physical activity without a threshold had demonstrated benefits of preventing diabetes [3,4]. A significant risk reduction was also confirmed in a previous meta-analysis with a lesser amount of exercise than the target of the existing guidelines [31]. Therefore, it is necessary to actively encourage sedentary postmenopausal women with lower exercise capacity to participate in physical activity even if the intensity is below the target range to achieve the benefits of diabetes prevention.

Interestingly, the results of our study did not provide clear evidence that exercising more than 1,500 MET-min/wk = 25 MET-hr/wk or exercising ≥6 day/wk reduced the risk of diabetes. The maximum effect was observed in postmenopausal women who moderately or vigorously exercised 4 to 5 days per week. In a study based on the Women's Health Initiative (WHI) cohort, a representative and large-scale multiethnic cohort of postmenopausal women, the upper tertile of exercise was associated with a lower risk of diabetes than the lower and middle tertiles [32]. Contrary to this, in the study by Hsia et al. [22] also using the WHI Cohort, the highest quintile (Q5) among Asians, who achieved more than 10.1 MET-hr/wk through walking or 23.5 MET-hr/wk with total physical activity, showed a trend for increased risk compared to the sedentary group, although the difference was not statistically significant. Asians in that study had a lower baseline BMI and waist circumference, fewer risk factors (e.g., drinking and smoking), and a higher proportion of individuals receiving hormone replacement therapy, which could be protective against diabetes, than the other ethnic groups. This trend for increasing risk with excessive exercise was inconsistent with previously reported meta-analyses

Table 4. IRs and multivariable-adjusted HRs (95% CI) of diabetes according to the number of days per week (day/wk) by intensity

No. of day/wk by intensity	No. of participants	No. of events	IR (per 1,000 person-years)	HR (95% CI)			
				Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
Premenopausal							
Vigorous							
0	628,022	26,353	5.13	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
1–3	225,267	8,783	4.75	0.93 (0.90–0.95)	0.93 (0.91–0.96)	0.95 (0.92–0.97)	0.97 (0.95–1.0)
4–5	50,718	1,899	4.56	0.89 (0.85–0.93)	0.87 (0.84–0.92)	0.89 (0.85–0.93)	0.92 (0.88–0.97)
≥6	22,800	1,061	5.68	1.10 (1.04–1.17)	1.01 (0.95–1.08)	1.02 (0.96–1.08)	1.03 (0.97–1.10)
Moderate							
0	550,754	23,409	5.2	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
1–3	276,509	10,603	4.68	0.90 (0.88–0.92)	0.94 (0.92–0.96)	0.95 (0.93–0.97)	0.98 (0.96–1.01)
4–5	65,907	2,570	4.75	0.91 (0.88–0.95)	0.92 (0.88–0.95)	0.93 (0.89–0.96)	0.97 (0.93–1.01)
≥6	33,637	1,514	5.49	1.06 (1.0–1.11)	1.01 (0.96–1.06)	1.01 (0.96–1.07)	1.01 (0.96–1.07)
Walking							
0	290,065	13,142	5.54	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
1–3	346,032	13,272	4.69	0.85 (0.83–0.87)	0.91 (0.87–0.93)	0.92 (0.90–0.94)	0.97 (0.94–0.99)
4–5	145,140	5,537	4.65	0.84 (0.81–0.87)	0.88 (0.86–0.91)	0.89 (0.87–0.92)	0.94 (0.91–0.97)
≥6	145,570	6,145	5.16	0.93 (0.90–0.98)	0.95 (0.92–0.98)	0.96 (0.93–0.99)	1.00 (0.97–1.03)
Postmenopausal							
Vigorous							
0	863,205	90,078	13.28	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
1–3	221,338	20,422	11.57	0.87 (0.86–0.88)	0.94 (0.92–0.95)	0.95 (0.93–0.96)	0.96 (0.95–0.98)
4–5	55,525	5,044	11.38	0.86 (0.83–0.88)	0.93 (0.91–0.96)	0.94 (0.91–0.97)	0.96 (0.93–0.99)
≥6	48,278	5,061	13.23	1.00 (0.97–1.02)	1.02 (1.0–1.05)	1.03 (1.0–1.06)	1.03 (1.0–1.06)
Moderate							
0	781,988	81,758	13.31	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
1–3	262,120	24,677	11.84	0.89 (0.88–0.90)	0.94 (0.93–0.96)	0.95 (0.94–0.97)	0.97 (0.96–0.99)
4–5	76,432	6,948	11.41	0.86 (0.84–0.88)	0.92 (0.90–0.94)	0.92 (0.90–0.95)	0.95 (0.92–0.97)
≥6	67,806	7,222	13.47	1.01 (0.99–1.04)	1.03 (1.01–1.06)	1.04 (1.01–1.06)	1.05 (1.03–1.08)
Walking							
0	444,550	47,333	13.57	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
1–3	345,070	33,371	12.22	0.90 (0.89–0.91)	0.94 (0.93–0.96)	0.95 (0.94–0.96)	0.97 (0.95–0.98)
4–5	162,310	15,231	11.82	0.87 (0.86–0.89)	0.92 (0.91–0.94)	0.93 (0.91–0.95)	0.94 (0.92–0.95)
≥6	236,416	24,670	13.23	0.98 (0.96–0.99)	0.99 (0.98–1.01)	0.99 (0.98–1.01)	1.00 (0.99–1.02)

IR, incidence rate; HR, hazard ratio; CI, confidence interval; MET, metabolic equivalent of task.

[a]Nonadjusted; [b]Adjusted for age; [c]Adjusted for age, low income, smoking, and drinking; [d]Adjusted for age, low income, smoking, drinking, hypertension, hyperlipidemia, body mass index, and baseline plasma glucose.

that found a dose-dependent nonlinear association between physical activity and type 2 diabetes, with the slope of risk reduction being pronounced with higher levels of physical activity [33,34]. The mean age was 64 years, the mean BMI was 24 kg/m^2, and the waist circumference was 77 cm in Asians in the WHI cohort, which are very similar to the baseline characteristics of the postmenopausal women in our study. In a study by Hu et al. [35] based on the Nurses' Health Study, another representative cohort of middle-aged women, a strong benefit of reducing the risk of diabetes in the highest quintile (Q5), with more than 21.8 MET-hr/wk of exercise, was attenuated after adjusting for BMI. In a trial comparing 150 minutes to 300 minutes of moderate to vigorous exercise in postmenopausal women, a higher amount of exercise was more effective for adiposity outcomes, although these dose-response effects were stronger for obese women (BMI ≥30 kg/m^2) than for nonobese women [19]. In a recent randomized controlled study that identified a correlation between lifestyle and glycemic health in women at high risk for diabetes, physical activity was not associated with better glycemic health among nonobese women after adjusting for correlated baseline risk factors, while a significant association was observed in obese women [36]. Based on these results, it is possible to infer that the effect of intense exercise on preventing diabetes in nonobese postmenopausal women is lower than that in obese women.

Patients with a nonobese type 2 diabetes phenotype are characterized by a disproportionate decrease in insulin secretion, more beta-cell dysfunction, and less insulin resistance than in obese patients [37], which is widely known as a component of the pathophysiology of type 2 diabetes [38]. Since intense exercise has a greater effect on improving insulin resistance than preserving insulin secretion [39], the benefits of intense exercise in preventing diabetes might be relatively low in nonobese Asian populations such as the participants of our study, who were relatively nonobese compared to those in other studies conducted in obese Western populations [20,32,35]. Excessive exercise produces little or no decrease in insulin secretion and causes hyperglycemia by increasing the secretion of catecholamines and cortisol, thereby affecting the feedback of the hypothalamic-pituitary-adrenal axis, inhibiting the action of insulin, and interfering with glucose utilization [39,40]. In addition, excessive exercise triggers multiorgan pathophysiology due to alterations in energy supply, amino acid imbalance (particularly glutamine reduction), oxidative stress, and inflammation through cytokine release [41,42]. These mechanisms might be related to beta-cell dysfunction and toxicity [43,44]. In a recent in vivo study, excessive exercise caused significant mitochondrial respiratory impairment, which coincided with loss of the Nrf2 protein and impaired glucose tolerance [45]. To date, no clinical study has investigated the threshold of excessive exercise that is disadvantageous for diabetes prevention. Considering that postmenopausal women with a high risk of diabetes are mostly elderly and have poor exercise capacity, it would be desirable to conduct research in the near future on the appropriate exercise intensity for diabetes prevention in postmenopausal women. Furthermore, it could be a good approach to individualize exercise intensity according to the severity of obesity and exercise ability.

The most important limitation of our study is that the reverse causality cannot be excluded because the risk of diabetes at baseline was inversely affected by the quantum of exercise, which was the exposure of the study. Our study did not adopt a randomized controlled design; instead, it used a model in which confounding factors were corrected as much as possible to compensate for this limitation. In addition, the median time of diabetes onset was longer than 8 years, which could also attenuate this statistical vulnerability. Second, the accuracy of the volume and frequency of exercise confirmed through the single-time health screening questionnaire could be insufficient, since it was not possible to additionally assess changes in exercise during follow-up. Third, it was impossible to consider other lifestyle factors such as diet, which is important for diabetes prevention, due to the lack of data in the cohort. Lastly, since this study only targeted Korean women, who are primarily East Asian, there may be differences in other ethnicities and regions.

In conclusion, exercise was effective in preventing diabetes in both premenopausal and postmenopausal women, even in small amounts of less than 500 MET-min/wk or just 1 day a week. Because of the relatively high prevalence of diabetes and the frequency of sedentary lifestyles, moderate exercise should be actively encouraged to lower the risk of diabetes in postmenopausal women while simultaneously considering the insignificant benefits of excessive exercise.

ARTICLE INFORMATION

Ethical statements
This study was approved by the National Health Insurance Service (NHIS) and the Institutional Review Board of Kangbuk Samsung Hospital (No. KBSMC 2021-04-049). The data are converted by deleting individuals' names and IDs and encrypted, so there is no risk of exposing individuals' personal information. Therefore, informed consent was not required.

Conflicts of interest
The authors have no conflicts of interest to declare.

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Author contributions
Conceptualization: JHC, JHY, KDH, EJR, WYL; Data curation: JHC, HMK, SEP, JHY, KDH; Formal Analysis: JHC, JHY, KDH; Funding acquisition: WYL; Investigation: JHC, HMK, SEP; Methodology: KDH, EJR, WYL; Project administration: KDH, EJR, WYL; Resources: KDH, EJR, WYL; Software: JHY, KDH; Supervision: EJR, WYL; Validation: HMK, SEP, JHY, KDH; Visualization: JHC; Writing–original draft: JHC, HMK, SEP, JHY; Writing–review&editing: KDH, EJR, WYL.
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